

Outcomes Pilot System Project Knowledge Acquisition Session Report

Session Date: October 09, 2003

Session Time: 4:00pm EST

Session Topic: User Requirements for a Cancer Outcomes System

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Session Location: DCP Offices, Rockville, MD

Type of Session:

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| <input type="checkbox"/> Interview | <input type="checkbox"/> Task Analysis | <input type="checkbox"/> Scenario Analysis |
| <input type="checkbox"/> Concept Analysis | <input type="checkbox"/> Observation | <input checked="" type="checkbox"/> Structured Interview |
| <input type="checkbox"/> Requirements Generation and Analysis | <input type="checkbox"/> Other: | |

Documentation: DCP Internet Supplemental Information, Appendix II: Instructions for Final Report (<http://www3.cancer.gov/prevention/pio/instruction.html>)

General Topic Area

The NCI Center for Bioinformatics (NCICB) is funding an effort to develop a technical solution to the problem of providing complete and reliable clinical study outcomes data to the cancer research community. Due to the large overall scope of developing a solution to collect, manage, report, and analyze clinical study outcomes data, the project has been divided into multiple phases. The focus of this Phase I effort is on gathering specific user data requirements and desired system functionality.

Report Summary

This report documents information gathered during a Knowledge Acquisition session with Dr. Leslie Ford, Acting Deputy Director and Associate Director for Clinical Research of the Division of Cancer Prevention (DCP). Dr. Ford is well known for the Breast Cancer Prevention Trial. This was the first study to definitively show (in April 1998) a medical intervention to decrease the incidence of a common cancer. The study found the drug tamoxifen reduces the incidence of breast cancer in women who are at high risk for this disease. Dr. Ford also helped to lead the NCI-funded study finding finasteride, the baldness drug, reduces risk of prostate cancer.

The DCP is the primary unit of the National Cancer Institute devoted to cancer prevention research. The core mission of this group is to conduct and support research designed to improve public health by decreasing cancer incidence, mortality, and morbidity. The DCP has championed definitive testing of discoveries in nutrition, chemoprevention, and molecular markers from a broad range of disciplines such as epidemiology, molecular biology, medical oncology, and clinical diagnostics. Definitive prevention and screening trials continue for a number of very high profile diseases such as cancers of the colon, lung, prostate, breast, ovary, cervix, and others.

Summary Findings

- Prevention studies strive to establish dosage levels with the most activity and the least toxicity. Most data supporting the DCP fall into the following categories: clinical trials, investigational plans, study subjects, and study evaluations. These data are collected in a variety of formats, including paper forms and manuscripts and electronic databases, across organizations. The DCP is currently improving capabilities to collect, store and retrieve outcomes data by aligning cooperative group agreements with outcomes data requirements and enhancing their enterprise database and information management system.
- The participant-level data for DCP studies reside with the IND holder. The IND holders for Phase III studies, the largest and longest prevention studies, are the cooperative groups. This will continue to be the arrangement unless the DCP supplements their existing staff with personnel to handle the workload associated with the larger studies.
- The cancer prevention vision is based on the premise that no one is totally healthy. Although this notion has been publicly accepted with regard to other diseases, it has not been accepted within the cancer care community. Oftentimes physicians and members of the general public are not aware of cancer markers and FDA-approved intervention drugs. This presents a challenge for the DCP in obtaining approval to study new prevention concepts and promoting prevention at the clinical level.
- The availability and use of prevention outcomes data are critical to achieving the cancer prevention vision. Outcomes data are the facts needed to convince researchers and the public of the potential benefits of adopting prevention interventions. In addition, further understanding of outcomes would promote acquisition of the resources needed to conduct studies for validating and reversing markers. Sharing outcomes across studies over time will promote the progress of cancer prevention.

Prevention Outcomes Data

The Nature of Prevention Outcomes

The nature of prevention outcomes data is better understood by comparing to other types of outcomes data and identifying the differences among outcomes data based on types and phases of prevention studies and the level of data collected by the parties involved in the studies.

There are basically two types of outcomes data: research outcomes and patient care outcomes. There are differences in these two types of outcomes data due to the differences in their respective measurements' purposes. The research goal is to know as much as possible about the intervention's affects in relation to the intervention's specifics, while the clinical measurement is focused on the participant's symptoms and disease's progress.

There are two types of research outcomes data: prevention outcomes and treatment outcomes. Differences in prevention outcomes and treatment outcomes exist due to the

differences in the respective goals of the two different types of studies. Treatment studies establish the maximum tolerated dose while prevention studies strive to establish dosage levels with the most activity and the least toxicity.

Research outcomes data are also variable based on the study's purpose. For example, early detection and screening trials determine cancer mortality ; phase I and II prevention studies, any biologic effect on cancerous tissue especially cancer marker regression; phase III prevention studies, reduction in adenoma instance and number of invasive cancers.

Researchers use prevention outcomes data to establish and validate findings in preventative care and feed future research initiatives. Prevention outcomes go beyond the measurement of the disease's occurrence or associated mortality to indicate disease suppression or marker regression. Prevention protocols measure markers, many of which can be very complex due to associations among markers and across observations. Prevention outcomes datasets are large and can extend over many years, making collection, storage and reporting of outcomes data an onerous task.

In studies sponsored by the DCP, prevention outcomes data are variable based on who is conducting the study. For example, studies conducted by consortia typically provide aggregate phase III data, while the DCP provides participant level data.

Prevention Outcomes Data Structure

DCP's data requirements, as described in consortia agreements, are categorized into these subject areas: clinical trial, investigational plan, study subject, and study evaluation. The subject areas are associated to one another through key data classes. Figure 1 depicts this data structure at a high level.

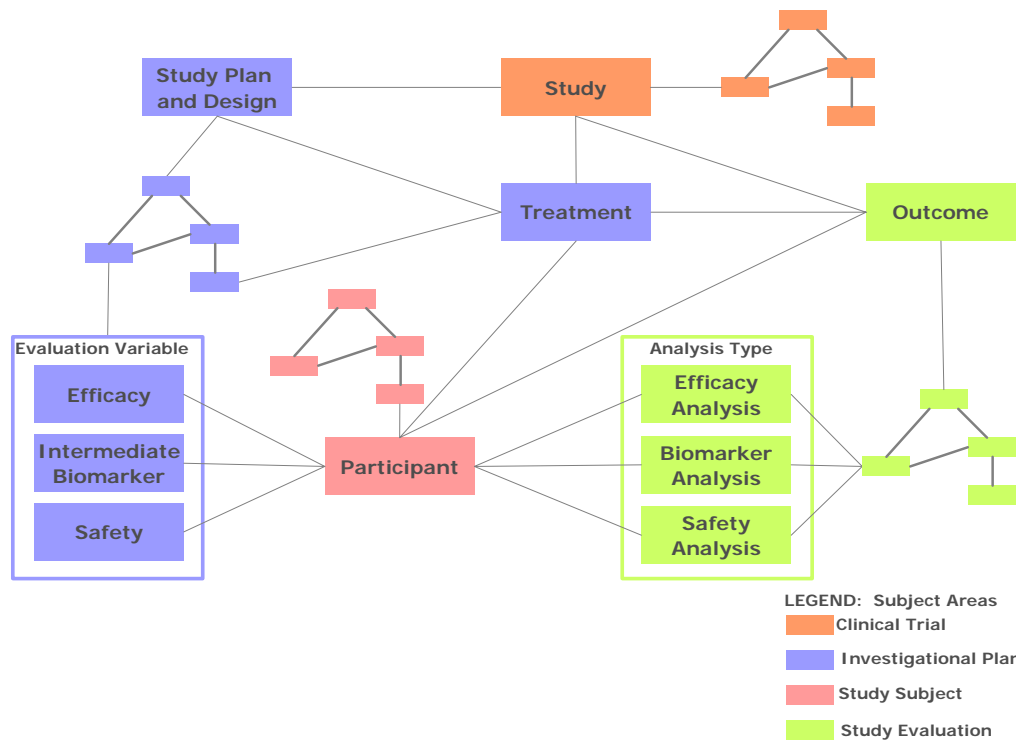


Figure 1. Prevention Outcomes Data Overview

The Clinical Trial subject area includes data about the study’s identifying characteristics, the study’s administrative characteristics, study objectives, test drugs/investigational products, and the study’s related features.

The Investigational Plan subject area includes data about study designs, study populations, treatments, evaluation variables (specifically efficacy, intermediate biomarkers, and safety), treatment outcomes, and adverse events.

The Study Subject subject area includes data about study participants, study subject dispositions, and protocol deviations.

The Study Evaluation subject area includes data about analysis methods, statistical issues, analysis comparisons, treatment compliance, evaluation group characteristics, and lab tests.

These four subject areas comprise all of the data required of the consortia conducting DCP-sponsored prevention studies. Some of this data is also required by federal agencies to monitor protocol execution and adverse events.

Availability of Prevention Outcomes Data

Outcomes data is available to the DCP; however it is not sufficiently accessible, comparable, or reliable to fully leverage the value of prevention research. The form of outcomes data limits the DCP’s access to data. Manuscript data and data tables are not easy to work with and usually do not provide all the data necessary to conduct evaluations. The DCP has access to varied levels of data depending on the study phase and involvement of cooperative

groups. Current organizational objectives are changing the way in which the DCP collects and uses outcomes data. Dr. Ford has initiated new projects to implement technologies and data reporting processes to improve the accessibility, security and usefulness of prevention outcomes data. The DCP is considering the requirements of the Health Insurance Portability and Accountability Act (HIPAA) as it continues to make changes with regard to data collection and retrieval.

Currently, study sites deliver a portion of outcomes data to the DCP. The DCP is beginning to collect more outcomes data from cooperative groups through agreements that require data to be submitted in a specific way. There is a project underway to make outcomes collected via Oracle Clinical's Remote Data Capture (OC-RDC) available in the DCP Enterprise System Knowledgebase (DESK). This system will provide the DCP with extended data in an easily accessible format.

The DCP ensures the proper use of submitted data by limiting access to approved personnel. Reporting outcomes prior to study completion is a sensitive issue because of a temptation to act on the data prior to the conclusion of the study. Another sensitive issue is the release of blinded data. During a study period, unblinded data should be viewed for safety reasons only.

The DCP only has access to individual participant-level data for Phase I and II DCP-sponsored studies. Knowing the number of patients accrued on DCP Phase I and II studies helps to give an idea of the amount of individual participant-level data available to the DCP. The DCP has formed a consortium with 5 to 10 institutions that can accrue up to 150 patients a year through the phase I and II studies. Typically there are no more than 20 active Phase I or II studies during the same time period.

Dr. Ford does not envision a point where participant-level outcomes data is made available by the cooperative groups. To give an idea of how much data this involves - these groups conduct Phase III studies accruing 16,000 to 32,000 participants over a 1 to 5 year time frame.

Serious Adverse Event (SAE) reporting is required at the participant-level. The cooperative groups notify the DCP of SAEs; however, the associated identifying participant information is not captured by the DCP. Another opportunity for the DCP to capture identifying participant information is at participant registration; however these data are collected through the Clinical Data Update System (CDUS) managed by the Cancer Therapy and Evaluation Program (CTEP) and are currently only used for tracking participant accruals.

Dr. Ford and her colleagues at DCP are concerned about the impact that the Health Insurance Portability and Accountability Act (HIPAA) could have on research. HIPAA is intended to protect the identity of persons involved in the medical care system, including research studies, and there is fear that the regulation has been over interpreted by the research community. At this point, HIPAA does not impact the management level of DCP data since the DCP rarely deals with data at the individual patient level.

The Cancer Prevention Vision

Cancer Prevention Awareness

The vision for cancer prevention is based on the premise no one is totally healthy. Given what is known about cancer's nature, it is conceivable that all people have a propensity to experience cancer. The public has accepted the idea that everyone has some likelihood of developing other diseases, such as heart disease, but it has not demonstrated the understanding that people can just as likely develop cancer. Figure 2 compares the public's acceptance of prevention of heart disease to that of cancer.

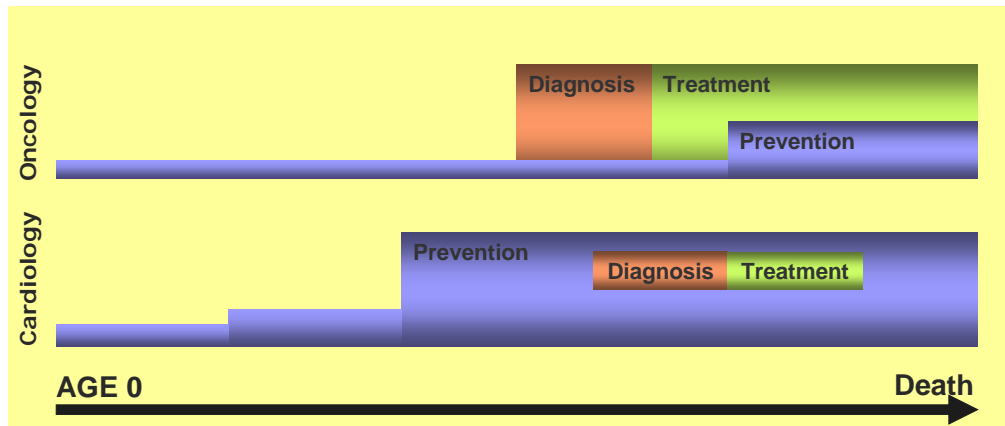


Figure 2. Prevention in Oncology vs. Cardiology

It may take a long time to develop a disease even though markers may be present from birth. For example, high cholesterol is not a disease; high cholesterol is one marker or risk factor for the onset of heart disease. High blood pressure is not a disease; it is a biomarker for increasing the risk of experiencing a heart attack. Once aware of a risk factor's presence, a person may willingly practice heart disease prevention by administering intervention drugs with known side effects. Others, understanding the likelihood of heart disease, may administer non-chemical interventions, such as diet and exercise, from an early age with an increasing emphasis as they grow older.

There are cancer markers such as high levels of K167 antigen and prostate intraepithelial neoplasias (PIN lesions) and, like with other diseases, there are intervention drugs with known side effects to prevent cancer. However, the public has not accepted cancer biomarkers and risk factors in a way that encourages the practice of cancer prevention. For the most part, the general public feels bio-chemical interventions to prevent cancer are not necessary until a real threat of cancer is present. There are FDA-approved cancer prevention drugs and many medical doctors are unaware of evolving cancer treatments and preventions. The public is even less aware.

The public has had a tendency to acknowledge some of the less invasive prevention practices. These practices, such as drinking green tea, eating broccoli and tomatoes, and taking herbal remedies, are considered "safe" but there are misconceptions about many of these prevention practices. Many preventions believed to be safe have not been proven to

prevent cancer without causing harm to the human body in other ways. Bad information on cancer prevention strategies can be easier to obtain than good information.

The DCP's Effort to Promote Cancer Prevention

Dr. Ford believes the cancer research community must approach cancer prevention as a collaborative effort in order to realize the vision for long term cancer prevention. Sharing outcomes data is critical to ongoing, successful collaboration. Dr. Ford identified the following issues in to achieving the cancer prevention vision:

- It is difficult to make the public and the FDA comfortable in moving prevention practices into a group of people who do not have cancer. This is an extension of the public belief that “healthy” people should not take “dangerous” drugs.
- Dr. Ford is working to affect patient care by educating researchers and clinicians about intraepithelial neoplasias (IENs) and biomarkers. Many researchers are not intimately familiar with the prevention study concept. Progress is being made, however. The prevention research paradigm is beginning to shift. Some people describe cancer prevention as “treating intraepithelial neoplasias (IEN)” meaning prevention’s goal is to reverse IENs. The IEN is a new genre of markers.
- Dr. Ford is creating and implementing pathways to communicate cancer prevention goals and persuade the public to practice prevention. Improved communication to the public and medical community requires a committed financial investment.

Applications of Prevention Outcomes Data

Outcomes data are valuable to both the researcher and the clinician in ways varying from influencing prevention research strategies to improving the patient care standard. Dr. Ford provided some ideas regarding the immediate uses of outcomes data including the following:

- Providing outcomes information to off-study participants will promote a better standard of care – in prevention and treatment.
- The DCP will use the outcomes system to plan and conduct studies designed to reverse cancer markers.
- The ability to access and apply outcomes data from numerous studies will make the process of validating markers more efficient.
- Analysis of aggregated prevention outcomes across studies and time will help to establish and document the timeline for prevention. This is important to developing future prevention research strategies that meet FDA approval.
- Sharing outcomes will enhance communication with medical professionals internal and external to the Cancer medical field. Knowledge of one disease’s outcomes is valuable to another disease’s research.
- Legacy research’s value will be augmented by reanalyzing historical outcomes data to update and/or validate early research results.

Entries for Domain Dictionary

Intermediate Biomarkers: Measurable parameters (histological, genetic, differentiation, proliferation or biochemical) which precede the formation of a malignant tumor. Biomarkers may be evaluated in clinical studies in three stages. The purpose of the first stage is to identify and evaluate biomarkers as predictors of increased cancer risk, *i.e.*, to establish the role of the biomarker in the etiology of the neoplasia under study. This involves determining if the biomarker is expressed differently in normal and high-risk tissue, is on or closely linked to the causal pathways for the cancer, can be measured quantitatively, reliably and accurately, and has a short latency compared to cancer. The next stage is to determine if the biomarker can be modulated by potential chemopreventive agents. Modulation by the study drug *vs.* placebo would then be evaluated as described above for efficacy. The final stage, validation of the biomarker as a surrogate endpoint for cancer in future studies, establishes that modulation of the biomarker correlates with decreased cancer incidence or increased latency.

Intraepithelial neoplasia (IEN): A precancerous, noninvasive lesion that may signal the onset of tumor development.